AD-A065 333 ARMY RESEARCH INST OF ENVIRONMENTAL MEDICINE NATICK MASS F/G 6/5
EVIDENCE FOR INCREASED INTRATHORACIC FLUID VOLUME IN MAN AT HIG--ETC(U)
SEP 78 J J JAEGER, J T SYLVESTER, A CYMERMAN

UNCLASSIFIED USARIEM-M-72/78 NL

1 OF 1
AD
A065333

END
DATE
FILMED
4-79
DDC

SECURITY CLASSIFICATION OF THIS PAGE (When Data Entered)

DDC

REPORT DOCUMENTATION PAGE

READ INSTRUCTIONS BEFORE COMPLETING FORM

1. REPORT NUMBER: M 72/78
2. GOVT ACCESSION NO.:
3. RECIPIENT'S CATALOG NUMBER:

4. TITLE (and Subtitle): Evidence for Increased Intrathoracic Fluid Volume in Man at High Altitude

5. TYPE OF REPORT & PERIOD COVERED:

6. PERFORMING ORG. REPORT NUMBER:

7. AUTHOR(s): J. J. Jaeger, J. T. Sylvester, A. Cymerman, J. T. Maher, J. J. Berberich, and J. C. Denniston

8. CONTRACT OR GRANT NUMBER(s):

9. PERFORMING ORGANIZATION NAME AND ADDRESS: U. S. Army Research Institute of Environmental Medicine, Natick, Massachusetts 01760

10. PROGRAM ELEMENT, PROJECT, TASK AREA & WORK UNIT NUMBERS: 6.27.77.A Defense Rsch Army 3E762777A845 74183051

11. CONTROLLING OFFICE NAME AND ADDRESS: U.S. Army Medical Research & Development Command, Fort Detrick, Frederick, MD 21701

12. REPORT DATE: 13 September 1978

13. NUMBER OF PAGES:

14. MONITORING AGENCY NAME & ADDRESS (if different from Controlling Office): Same

15. SECURITY CLASS. (of this report): Unclassified

15a. DECLASSIFICATION/DOWNGRADING SCHEDULE:

LEVEL II

16. DISTRIBUTION STATEMENT (of this Report): Distribution of this document is unlimited.

12 27p.

DDC RECEIVED MAR 6 1979 C

17. DISTRIBUTION STATEMENT (of the abstract entered in Block 20, if different from Report): NA

14 USARIEM-M-72/78

18. SUPPLEMENTARY NOTES: NA

19. KEY WORDS (Continue on reverse side if necessary and identify by block number): alveolar-arterial O_2 gradient, closing capacity, high altitude pulmonary edema, lung volumes, transthoracic electrical impedance, transpulmonary pressure

20. ABSTRACT (Continue on reverse side if necessary and identify by block number): To determine if subclinical pulmonary edema occurs commonly at high altitude, 25 young male soldiers participated in a strenuous, 72 h field exercise at low altitude (200 to 875 m) and in a similar exercise one week later at high altitude (3000 to 4300 m). At 0, 36, and 72 h of each phase the subjects were given a physical examination, a chest radiograph was taken, and the following measurements were made: total lung capacity, forced vital capacity, residual volume, closing capacity, slope of phase III of the nitrogen washout curve, transthoracic electrical impedance, and

DD FORM 1 JAN 73 1473 EDITION OF 1 NOV 65 IS OBSOLETE

040 850 LB

SECURITY CLASSIFICATION OF THIS PAGE (When Data Entered)

DDC FILE COPY AD A065333

20. (Contd)

the quasi-static relationship between transpulmonary pressure and lung volume (PV curve). At 0 and 72 h of each phase, arterial P_{O_2}, P_{CO_2} and pH were measured and physiological dead space (V_D/V_T), and the alveolar-arterial O_2 gradient (A-a D_{O_2}) calculated. No evidence of pulmonary edema was obtained from physical examination or chest radiographs. Relative to the low altitude values, immediate and sustained decreases in vital capacity and impedance, and a clockwise rotation of the PV curve occurred at high altitude. In contrast, closing capacity and residual volume did not change upon arrival at high altitude, but increased later during the exposure. There was no effect of altitude upon A-a DO_2, V_D/V_T or the slope of phase III. These observations upon arrival at high altitude followed by a gradual increase in extravascular fluid volume in the peribronchial spaces of dependent lung regions. These changes if present were apparently not sufficient to impair gas exchange or alter the distribution of ventilation.

Evidence for Increased Intrathoracic Fluid Volume in Man at High Altitude

Running Title: Intrathoracic Fluid at High Altitude

J. J. Jaeger, J. T. Sylvester, A. Cymerman
J. T. Maher, J. J. Berberich, and J. C. Denniston

U.S. Army Research Institute of Environmental Medicine
Natick, Massachusetts 01760

Address correspondence to: James J. Jaeger
Division of Medicine
WRAIR, WRAMC
Washington, DC 20012

Address reprint requests to: J. T. Maher
U.S. Army Research Institute
of Environmental Medicine
Natick, MA 01760

Abstract

To determine if subclinical pulmonary edema occurs commonly at high altitude, 25 young male soldiers participated in a strenuous, 72 h field exercise at low altitude (200 to 875 m) and in a similar exercise one week later at high altitude (3000 to 4300 m). At 0, 36, and 72 h of each phase the subjects were given a physical examination, a chest radiograph was taken, and the following measurements were made: total lung capacity, forced vital capacity, residual volume, closing capacity, slope of phase III of the nitrogen washout curve, transthoracic electrical impedance, and the quasi-static relationship between transpulmonary pressure and lung volume (PV curve). At 0 and 72 h of each phase, arterial P_{O_2}, P_{CO_2} and pH were measured and physiological dead space (V_D/V_T), and the alveolar-arterial O_2 gradient (A-a D_{O_2}) calculated. No evidence of pulmonary edema was obtained from physical examination or chest radiographs. Relative to the low altitude values, immediate and sustained decreases in vital capacity and impedance, and a clockwise rotation of the PV curve occurred at high altitude. In contrast, closing capacity and residual volume did not change upon arrival at high altitude, but increased later during the exposure. There was no effect of altitude upon A-a DO_2, V_D/V_T or the slope of phase III. These observations are consistent with an abrupt increase in thoracic intravascular fluid volume upon arrival at high altitude followed by a gradual increase in extravascular fluid volume in the peribronchial spaces of dependent lung regions. These changes if present were apparently not sufficient to impair gas exchange or alter the distribution of ventilation.

-A-

alveolar-arterial O_2 gradient, closing capacity, high altitude pulmonary edema, lung volumes, transthoracic electrical impedance, transpulmonary pressure.

Introduction

High altitude pulmonary edema can be a life-threatening complication of acute altitude exposure. Although the incidence of this disease is low (15), it has been suggested that interstitial edema which does not progress to clinically apparent intraalveolar edema, develops in most individuals who ascend rapidly to high altitude (17,19,26). The objective of this study was to determine if subclinical pulmonary edema was a common occurrence among non-acclimated men abruptly exposed to an altitude of 3000 to 4300 m. Since high altitude pulmonary edema has often been associated with physical exertion during or following rapid ascent (8,13), strenuous exercise was included in the experimental design. Due to the anticipated difficulties in detecting mild pulmonary edema, we employed a relatively large number of test subjects and a paired comparison, repeated measures statistical design.

Methods

Subjects. Twenty-five healthy, male soldiers from the 10th Special Forces Group stationed at Ft. Devens, MA participated in this study. Informed, voluntary consent was obtained from all subjects. The mean age of the subjects was 26 years with a range of 18 to 38 years. Fifteen subjects were smokers with an average consumption of 8.0 pack-years (packs per day multiplied by number of years subject smoked). No subject had a history of cardiopulmonary disease. Three days before the start of the experiment the subjects were given a physical examination, briefed on all aspects of the study and trained to perform the various ventilatory maneuvers required.

Study Outline. The experiment consisted of a low altitude phase and a high altitude phase each of which was 72 h in duration. During the low altitude phase the subjects walked a total distance of 84 km with heavy packs (approximately 20-50 kg) in the White Mountains of New Hampshire at elevations from 200 to 875 m above sea level. The subjects were in the field for the entire 72 h period, prepared their own rations, and performed various simulated military tasks at prescribed times and locations. Between stops the average rate of movement was 3 km h^{-1}. One week later the same subjects were flown to Colorado Springs, CO, and within 3 h, began another simulated military exercise at high altitude. This phase consisted of two 15 km hikes from the 3000 to the 4300 m elevations of Pikes Peak, CO. The average rate of movement between stops at high altitude was 1.8 km h^{-1}. The actual routes followed by the soldiers in both the low altitude and the high altitude phases were chosen by their commanders to be as similar as possible in degree of difficulty, considering both the linear distance covered and the amount of climbing performed. Physiological measurements were made at 0, 36, and 72 h during each phase. The measurements were made at an elevation of 200 m during the low altitude phase, and at an elevation of 4300 m during the high altitude phase. The individual measurements and tests are described below.

Physical Examination and Chest Radiographs. Subjects were asked about symptoms and were given a physical examination using a standardized format. Posterior-anterior and lateral chest radiographs were taken at full inspiration with the subject standing. The same portable X-ray unit (General Electric Mobile EP 300) was used throughout the study. A baseline radiograph was obtained 3 days before the start of the low altitude phase of the study. At the completion

of the experiment the six radiographs obtained at the low and high altitude testing sessions were compared to the baseline film by a radiologist who was aware of the chronological sequence of the films but unaware of the altitude at which they were taken. Each radiograph was examined for specific findings of pulmonary edema (peribronchial cuffing, Kerley lines, alveolar infiltrates, pleural effusion, thickening of intralobar fissures), and pulmonary vascular congestion. The findings were graded as definite, probable or possible. In addition, cardiac and thoracic widths on the posterior-anterior film were measured and their ratio calculated.

Lung Volumes and Quasi-Static Transpulmonary Pressure-Volume Curve. During each testing session, the subjects swallowed a balloon-tipped catheter which was then positioned in the lower esophagus approximately 15 cm above the diaphragm. The esophageal balloon was 10 cm long and was filled with 0.5cc of air. Balloons were checked routinely for leaks and correct volume. With the balloon in place, the subjects performed single-breath nitrogen washout maneuvers as outlined by Buist and Ross (2). Inspired and expired flow were controlled by the subjects at 0.3 to 0.4 L sec^{-1} by reference to an analog flowmeter display. During these maneuvers simultaneous recordings of nitrogen concentration versus volume, and volume versus transpulmonary pressure were made using two X-Y recorders. Inspired and expired volumes were measured by a dry, rolling seal spirometer (Cardio-Pulmonary Instruments). Transpulmonary pressure (esophageal pressure minus mouth pressure) was measured by a differential transducer (Statham PM-6). Nitrogen concentration was measured with a nitrogen analyzer (Cardio-Pulmonary Instruments). Although linear at low altitude, this analyzer was found to be significantly alinear at high altitude, presumably because of the lower density of air. Therefore, nitrogen measurements obtained at high altitude were corrected

by a factor determined from a 4-point calibration procedure using analyzed gases with nitrogen concentrations between 0 and 30%. At each testing session, the subjects performed a minimum of 3 and a maximum of 5 single-breath nitrogen washout maneuvers. These maneuvers were judged acceptable when inspired and expired flow was maintained between 0.3 to 0.4 L sec^{-1}, inspired vital capacity did not differ from expired vital capacity by more than 5%, and the transpulmonary pressure-volume record was free from esophageal contraction artifact. From the records of expired nitrogen concentration versus expired volume the following lung volumes were calculated as described by Buist and Ross (2): total lung capacity, residual volume, and closing capacity. In addition, the slope of phase III of the nitrogen washout curve was calculated. From the records of expired volume versus transpulmonary pressure and the calculated values for total lung capacity, quasi-static pressure-volume relationships were obtained by determining lung volume at transpulmonary pressure intervals of 2.5 cm of water between 0 and 30 cm of water. The values for the parameters obtained from acceptable records from each subject at each testing session were averaged for use in the statistical analysis.

Without the esophageal balloon in place, the subjects also performed 3 to 5 forced vital capacity maneuvers using a 9 liter, water-filled spirometer (W.E. Collins). The subjects' best effort, defined as the spirogram with the largest vital capacity, was used in the data analysis.

Transthoracic Electrical Impedance. Transthoracic electrical impedance was measured at each testing session using four aluminized mylar tape electrodes and a Minnesota Impedance Cardiograph (Model 304A). A constant sinusoidal current (4mA rms) at 100 k hz was applied to two outer electrodes, one on the

neck and the other around the abdomen. Changes in potential which reflect changes in impedance were measured from two inner electrodes, one around the neck and one around the lower thorax (5). Measurements were made at total lung capacity with the subject standing following a 5 min rest period. Reproducible electrode placement was insured by marking the subjects with indelible ink during a preliminary testing session.

Ventilatory Parameters. At 0 and 72 h of the low and high altitude phases, an arterial blood sample was drawn from the brachial or radial artery using a heparinized glass syringe and a 20 gauge needle with the subject supine. Local anesthesia (1% lidocaine) was used at the puncture site. Samples were analyzed for pH, P_{CO_2} and P_{O_2} using a calibrated blood gas analyzer (Radiometer Model BMS3-MK2). Immediately before or after this procedure, expired air was collected for 3 min via a two-way "J" valve into a meteorological balloon. The volume of expired gas was measured with a spirometer (W. E. Collins) and its O_2 and CO_2 concentrations with gas analyzers (Beckman OM-11 and LB-2). From these measurements resting ventilation, physiological dead space, respiratory exchange ratio, alveolar P_{O_2} and the alveolar-arterial gradient for oxygen were calculated. Respiratory frequency was measured during the collection of expired gas.

Statistical Methods. Statistical analysis of the data was accomplished by either a 2-way or a 3-way analysis of variance as appropriate using a repeated measures design. Variance ratios are reported for the main treatment effects of altitude and time and for the interaction of altitude and time. Effects were considered significant when variance ratios exceeded the significance limit "F" value for $P \leq 0.05$. When the interaction variance ratio was not statistically significant, main treatment effects were interpreted in a straightforward manner.

When the interaction variance ratio was significant, the variable analyzed was judged to be a different function of time at low altitude than at high altitude and main treatment effects were disregarded.

As is noted in the data to follow, n is not equal to 25 for all parameters. In a few instances there were unavoidable test subject absences for one or more tests. A few subjects were not able to swallow the esophageal balloon on all six testing sessions. Although attempted, arterial blood was not obtained from all subjects when scheduled. There were occasional equipment malfunctions. Only those subjects from whom a complete set of data had been obtained for a particular parameter were included in the analysis.

Results

Physical Examination and Chest Radiographs. Symptoms reported by the test subjects at low altitude generally reflected the strenuous nature of the simulated military operation with the largest number of subjects reporting symptoms at the 36 h testing session (Table 1). These same symptoms were also reported during the high altitude phase but by many more subjects and at all three testing sessions. Once again there was a large increase in the number of subjects reporting symptoms at the 36 h testing session. Of particular note is the increased frequency of headache, nausea, vomiting, dizziness, and anorexia at high altitude suggesting the development of acute mountain sickness in a large number of subjects (6). In addition, symptoms compatible with, but not specific for, high altitude pulmonary edema (dyspnea at rest and exercise, cough, wheezing, orthopnea) were also more frequently reported at high altitude.

On physical examination (Table 2), pulmonary edema was not present in any subject as judged by the absence of rales and wheezing. However, an accentuated

pulmonic component of the second heart sound and a gallop heart rhythm were heard in a number of subjects at high altitude suggesting the occurrence of pulmonary hypertension.

A complete set of chest radiographs was obtained on 12 subjects. No definite abnormalities were observed at any time. There were 2 probable findings of peribronchial cuffing but both were observed during the low altitude phase of the study. In addition, 1 probable (low altitude) and 7 possible (2 at low and 5 at high altitude) findings compatible with pulmonary vascular congestion were observed. There was no significant change in the ratio of cardiac width to thoracic width. The mean and standard error for this parameter was 0.41 ± 0.01.

Ventilatory Parameters. The effects of altitude exposure on the ventilatory parameters are shown in Table 3. Resting minute ventilation ($\dot{V}_E$) at 0 h was the same at both low and high altitude but subsequently increased with time at high altitude while the low altitude values did not change. The increase in $\dot{V}_E$ at high altitude was due primarily to an increase in tidal volume, since there were no significant changes in respiratory frequency. Both $P_{a_{O_2}}$ and $P_{a_{CO_2}}$ were significantly lower at high altitude than at low altitude. At both altitudes $P_{a_{O_2}}$ tended to increase and $P_{a_{CO_2}}$ to decrease with time. Arterial pH at 0 h at high altitude was greater than the low altitude value and increased further with time. At low altitude, pH did not change. There were no significant differences noted for the ratio of physiological dead space to tidal volume. The alveolar-arterial gradient for oxygen decreased with time at both low and high altitude but did not change as a function of altitude.

Lung Volumes and Quasi-Static Transpulmonary Pressure-Volume Curves. The effects of high altitude exposure on lung volumes are shown in Table 4. Forced

vital capacity was less at high altitude than at low altitude at all times. Although total lung capacity was not affected by altitude, it increased significantly with time during both the low and high altitude phases of the study. There was a significant and progressive increase in residual volume measured at 4300 m relative to that observed at 200 m. Closing capacity increased with time at both altitudes and the increase was greater at high altitude than at low altitude. The slope of phase III of the nitrogen washout curve increased slightly with time but did not change as a function of altitude (Table 4).

Acceptable expiratory pressure-volume curves at all 6 testing sessions were obtained from 11 subjects. From these records, lung volume was analyzed as a function of transpulmonary pressure, altitude, and time using a 3-factor, repeated measures analysis of variance. This analysis revealed that lung volume was a significantly different function of transpulmonary pressure at high altitude than at low altitude (variance ratio=3.24, $p \leq 0.001$) while volume as a function of pressure was not significantly changed by time. These data are represented graphically in Figure 1, in which the pressure-volume relationships at low and high altitude, averaged across time, are shown. It is seen that the pressure-volume curve obtained at high altitude is rotated clockwise with respect to the low altitude curve.

Transthoracic Electrical Impedance. Since transthoracic impedance was measured at total lung capacity and since changes in this lung volume occurred with time at both low and high altitude, the values of impedance were normalized by expressing them as ohms per liter of total lung capacity. Impedance per unit lung volume was lower at high altitude than at low altitude and tended to decrease with time at both altitudes (Table 4).

Discussion

Transthoracic electrical impedance was reduced at high altitude (Table 4). Similar changes have been shown to accompany experimentally-produced increases in thoracic fluid volumes in both humans and animals (24,25). In addition, decreased impedance has previously been reported in humans at high altitude (27) and, more recently, impedance has been correlated with the progression and regression of high altitude pulmonary edema (12).

The immediate and sustained decrease in forced vital capacity which we observed at high altitude has also been previously reported (31). It has long been recognized that vital capacity is reduced by pulmonary edema and congestion caused by left heart failure (1). Vital capacity is also reduced during acute pulmonary congestion caused by intravenous administration of fluids (4) and negative pressure breathing (22). The mechanism of this reduction probably involves not only the greater occupation of space in the thorax by an increased volume of fluid, but also a change in the mechanical properties of the lungs (1).

The clockwise rotation of the transpulmonary pressure-volume curve which occurred at high altitude (Figure 1) suggests a stiffer, less compliant lung. Similar changes have been observed in humans when thoracic blood volume was increased by lowering intrathoracic pressure (9) and in animals during experimentally-produced congestion and edema (3,7).

Thus, the changes in impedance, vital capacity and the pressure-volume curve observed at high altitude are consistent with an increase in thoracic fluid volume which occurred immediately upon arrival and persisted for the remainder of the sojourn. On the basis of these measurements alone, it is not possible to speculate whether the increase in fluid volume was purely extravascular or whether

it was both extravascular and intravascular. Certainly, an increase in central blood volume due to pulmonary hypertension induced by hypoxia would not be unexpected (16,19,28,32). The findings of an accentuated pulmonic component of the second heart sound and a gallop heart rhythm in several subjects at high altitude are consistent with this expectation (Table 2). But is an increase in extravascular fluid volume a reasonable possibility?

In our subjects, closing capacity and residual volume increased at high altitude (Table 4), suggesting the development of premature closure of small airways in dependent lung regions. A well-documented cause of premature small airway closure is the accumulation of pulmonary edema fluid in the peribronchial spaces of the lung (11,14,21,23). Staub et al. (29) have demonstrated that these spaces are the first sites of fluid accumulation in the development of pulmonary edema. Thus, the changes in closing capacity and residual volume are consistent with an increase in lung extravascular fluid volume.

In contrast to impedance, vital capacity and the pressure-volume curve, residual volume and closing capacity were not changed immediately upon arrival at high altitude (Table 4). Significant increases in these volumes did not occur until later. On this basis, we propose the following sequence of events as one possible explanation of our findings. Upon arrival at high altitude, there was an abrupt increase in central blood volume due to pulmonary hypertension induced by hypoxia. The increased blood volume caused immediate decreases in transthoracic electrical impedance and forced vital capacity and the clockwise rotation of the transpulmonary pressure-volume curve. Subsequently, because of sustained elevations in intravascular pressures, there was a slow accumulation of fluid in the peribronchial and perivascular spaces of dependent lung regions, which resulted

in the gradual development of premature airway closure and thus increases in closing capacity and residual volume.

Dyspnea, cough, wheezing and orthopnea were reported by the subjects more frequently at high altitude than at low altitude. These symptoms are compatible with, but of course not specific for, pulmonary edema. On physical examination, no signs of pulmonary edema were present and no definite radiographic evidence of fluid accumulation in the lungs was found. Moreover, the radiographic findings of edema and congestion classified as "probable" or "possible" were few and seemed to be randomly distributed between the low and high altitude films. Thus, if pulmonary edema occurred at high altitude, it was too mild to be detectable by physical examination or chest radiography.

The lack of significant change in the alveolar-arterial oxygen gradient and in the dead space to tidal volume ratio indicates that pulmonary edema, if present, was not sufficient to cause significant deterioration in gas exchange. Previous measurements of the A-a O_2 gradient at high altitude have been inconsistent (18,19,26). Kronenburg et al. (19) found an increase in V_D/V_T after acute exposure to high altitude. We cannot explain the difference between our results and theirs.

The slope of phase III of the single-breath N_2 washout curve was not altered by high altitude exposure (Table 4), suggesting no significant change in the distribution of ventilation. Gray et al. (10) and Sutton et al. (30), in contrast, reported significant increases in this variable. This discrepancy may possibly be explained by the alinearity of the N_2 analyzer which we observed at high altitude. Had we not corrected for this alinearity, we also would have obtained a significant increase in the slope of phase III at high altitude.

It is of parenthetical interest that total lung capacity, although uninfluenced

by altitude, underwent a significant increase with respect to time (Table 4). We have no explanation for this phenomenon other than to suggest that the increased ventilation demanded by the prolonged exertion of the hikes may have altered the mechanical or reflex properties of the chest wall. Leith and Bradley (20) observed similar increases in TLC in humans performing maneuvers intended to increase ventilatory muscle strength.

Finally, it should be emphasized that none of our measurements constitute direct evidence for an increase in lung fluid volume. At present, it is not possible to obtain such evidence from human subjects. Thus, the postulation that lung fluid volume increases at high altitude, although plausible, remains unproved.

Acknowledgement

The authors are indebted to the soldiers from the 10th Special Forces Group for their enthusiastic participation in this arduous study.

We also thank Dr. F. Stitik, Department of Radiology, Johns Hopkins University Hospital, for the detailed analysis of the radiographs.

The views, opinions, and/or findings contained in this report are those of the author(s) and should not be construed as an official Department of the Army position, policy, or decision, unless so designated by other official documentation.

Human subjects participated in these studies after giving their free and informed voluntary consent. Investigators adhered to AR 70-25 and USAMRDC Regulation 70-25 on Use of Volunteers in Research.

Current addresses of the authors are as follows: J. J. Jaeger, Division of Medicine, Walter Reed Army Institute of Research, Washington, DC 20012; J. T. Sylvester, Department of Medicine, Johns Hopkins University Hospital, Baltimore, MD 21205; J. J. Berberich, University of Miami School of Medicine, Miami, FL 33152; J. C. Denniston, Aeromedical Activity, Army Aeromedical Center, Ft. Rucker, AL 36362.

References

1. Briscoe, W. A. Lung volumes. In: Handbook of Physiology. Respiration. Washington, DC: Am. Physiol. Soc., 1965, sect. 3, vol. 2, chapt. 53, p. 1345-1379.

2. Buist, A. S., and B. B. Ross. Predicted values for closing volumes using a modified single-breath nitrogen test. Am. Rev. Respirat. Dis. 107:744-752, 1973.

3. Cook, C. D., J. Mead, G. L. Schreiner, N. R. Frank, and J. M. Craig. Pulmonary mechanics during induced pulmonary edema in anesthetized dogs. J. Appl. Physiol. 14:177-186, 1959.

4. Cournand, A., and D. Richards. Pulmonary insufficiency. I. Discussion of a physiological classification and presentation of clinical test. Ann. Rev. Tuberc. 44:26-41, 1941.

5. Denniston, J. C., J. T. Maher, J. T. Reeves, J. C. Cruz, A. Cymerman, and R. F. Grover. Measurement of cardiac output by electrical impedance at rest and during exercise. J. Appl. Physiol. 40:91-95, 1976.

6. Evans, W. O., S. M. Robinson, D. H. Horstman, R. E. Jackson, and R. B. Weiskopf. Amelioration of the symptoms of acute mountain sickness by staging and acetazolamide. Aviat. Space Environ. Med. 47:512-516, 1976.

7. Frank, N. R. Influence of acute pulmonary vascular congestion on recoiling force of excised cats' lung. J. Appl. Physiol. 14:905-908, 1959.

8. Fred, H. L., A. M. Schmidt, T. Bates, and H. H. Hecht. Acute pulmonary edema of altitude: clinical and physiologic observations. Circ. 25:929-937, 1962.

9. Goldberg, H. S., W. Mitzner, K. Adams, H. Menkes, S. Lichtenstein, and S. Permutt. Effect of intrathoracic pressure on pressure-volume characteristics of the lung in man. J. Appl. Physiol. 38:411-417, 1975.

10. Gray, G. W., D. M. McFadden, C. S. Houston, and A. C. Bryan. Changes in the single-breath nitrogen washout curve on exposure to 17,600 feet. J. Appl. Physiol. 39:652-656, 1975.

11. Harken, A. H., and N. E. O'Connor. The influence of clinically undetectable pulmonary edema on small airway closure in the dog. Ann. Surg. 184:183-188, 1976.

12. Hoon, R. S., V. Balasubramanian, S. C. Tiwari, O. P. Mathew, A. Behl, S. C. Sharma, and K. S. Chadha. Changes in transthoracic electrical impedance at high altitude. Br. Heart J. 39:61-66, 1977.

13. Houston, C. S. Acute pulmonary edema of high altitude. N. Eng. J. Med. 263:478-480, 1960.

14. Hughes, J. M. B., and D. Y. Rosenzweig. Factors affecting trapped gas volume in perfused dog lungs. J. Appl. Physiol. 29:332-339, 1970.

15. Hultgren, H. N. High altitude pulmonary edema. Adv. Cardiol. 5:24-31, 1970.

16. Hultgren, H. N., and R. F. Grover. Circulatory adaptation to high altitude. Ann. Rev. Med. 19:119-152, 1968.

17. Kleiner, J. P., and W. P. Nelson. High altitude pulmonary edema. J. Am. Med. Assn. 234:491-495, 1975.

18. Kreuzer, F., S. M. Tenney, D. C. Andresen, B. F. Schreiner, R. E. Nye, Jr., J. C. Mithoefer, H. Valtin, and A. Naitoue. Alveolar-arterial oxygen gradient in the dog at altitude. J. Appl. Physiol. 15:796-800, 1960.

19. Kronenberg, R. S., P. Safar, J. Lee, F. Wright, W. Noble, E. Wahrenbrock, R. Hickey, E. Nemoto, and J. W. Severinghaus. Pulmonary artery pressure and alveolar gas exchange in man during acclimatization to 12,470 feet. J. Clin. Invest. 50:827-837, 1971.

20. Leith, D. E., and M. Bradley. Ventilatory muscle strength and endurance training. J. Appl. Physiol. 41:508-516, 1976.

21. Lemen, R., J. G. Jones, P. D. Graf, and G. Cowan. "Closing volume" changes in alloxan-induced pulmonary edema in anesthetized dogs. J. Appl. Physiol. 39:235-241, 1975.

22. Mills, J. N. The influence upon the vital capacity of procedures calculated to alter the volume of blood in the lungs. J. Physiol. (London) 110:207-216, 1949.

23. Muir, A. L., D. C. Flenley, B. J. Kirby, M. F. Sudlow, A. R. Guyatt, and H. M. Brash. Cardiorespiratory effects of rapid saline infusion in normal man. J. Appl. Physiol. 38:786-793, 1975.

24. Pomerantz, M., R. Baumgartner, J. Lauridsan, and B. Eiseman. Transthoracic electrical impedance for the early detection of pulmonary edema. Surgery 66:260-268, 1969.

25. Pomerantz, M., F. Delgado, and B. Eiseman. Clinical evaluation of transthoracic electrical impedance as a guide to intrathoracic fluid volumes. Ann. Surg. 171:686-691, 1970.

26. Reeves, J. T., J. Halpin, J. E. Cohn, and F. Daoud. Increased alveolar-arterial oxygen difference during simulated high-altitude exposure. J. Appl. Physiol. 27:658-661, 1969.

27. Roy, S. B., V. Balasubramanian, M. R. Khan, V. S. Kaushik, S. C. Manchanda, and S. K. Guha. Transthoracic electrical impedance in cases of high-altitude hypoxia. Br. Med. J. 3:771-775, 1974.

28. Saltz, S. B., G. A. Beller, S. R. Giamber, and J. S. Alpert. Circulatory response to acute hypobaric hypoxia in conscious dogs. Aviat. Space Environ. Med. 47:129-132, 1976.

29. Staub, N. C., H. Nagano, and M. L. Pearce. Pulmonary edema in dogs, especially the sequence of fluid accumulation in lungs. J. Appl. Physiol. 22:227-240, 1967.

30. Sutton, J. R., G. W. Gray, M. D. McFadden, A. C. Bryan, E. S. Horton, and C. S. Houston. Nitrogen washout studies in acute mountain sickness. Aviat. Space Environ. Med. 48:108-110, 1977.

31. Tenney, S. M., H. Rahn, R. C. Stroud, and J. C. Mithoefer. Adaptation to high altitude: changes in lung volumes during the first seven days at Mt. Evans, Colorado. J. Appl. Physiol. 5:607-613, 1953.

32. Vogel, J. H. K., J. E. Goss, M. Mori, and H. L. Brammell. Pulmonary circulation in normal man with acute exposure to high altitude (14,260 feet). Circ. 34(suppl. III):233, 1966.

Table 1. Numbers of subjects reporting symptoms at low and high altitude (n=25)

Symptom	Phase					
	Low Altitude			High Altitude		
	0 h	36 h	72 h	0 h	36 h	72 h
Fatigue		3	4	18	19	10
Weakness		3		1	12	
Chills		2		1	12	
Sweats		1			1	
Fever					1	
Headache		5		5	21	5
Dizziness		1		13	8	1
Visual disturbance					2	
Rhinorrhea		2		3	12	8
Epistaxis					1	1
Sore throat					3	
Dyspnea at rest				3	12	2
Dyspnea with exercise				3	21	
Cough		2			7	3
Sputum production						2
Wheezing					1	2
Chest pain					1	
Palpitations				1		1
Orthopnea					7	
Anorexia		3	1	1	14	1
Nausea		2		6	12	
Vomiting					3	
Abdominal pain		1				
Diarrhea		1	1	1	2	
Constipation					2	
Inability to solve problems		2			13	4
Impaired memory				3	5	3
Syncope					2	
Insomnia					1	
Tinnitus	1				1	1
Foot blisters		8	4			

Table 2. Numbers of subjects exhibiting abnormalities at low and high altitude (n=25)

Physical Finding	Phase					
	Low Altitude			High Altitude		
	0 h	36 h	72 h	0 h	36 h	72 h
Wheezing						
Rales						
Ronchi					1	
Cyanosis				12	23	8
Arrhythmia					1	
Accentuated P_2*					5	3
Gallop heart rhythm					4	
Heart murmur		1			1	

*pulmonic component of the second heart sound.

Table 3. Resting ventilation, respiratory frequency, blood gases, pH, physiological dead space to tidal volume ratio (V_D/V_T) and the alveolar-arterial O_2 gradient (A-a DO_2) at low and high altitude

Parameter	Phase						Variance Ratio		
	Low Altitude			High altitude					
	0 h	36 h	72 h	0 h	36 h	72 h	Altitude	Time	Interaction
Resting Ventilation ($L\ min^{-1}$)	9.04±0.30	10.25±0.57	9.08±0.47	9.97±0.37	12.77±0.59	12.47±0.76	29.37*	9.43*	5.22*
Respiratory frequency(min^{-1})	13 ±1	13 ±1	13 ±2	14 ±1	13 ±2	13 ±1	<1	<1	<1
$P_{a_{O_2}}$ (mm Hg)	91.9±2.1		95.5±2.4	39.5±0.9		45.1±0.9	890.97*	25.84*	< 1
$P_{a_{CO_2}}$ (mm Hg)	34.6±0.6		33.3±0.5	30.1±0.4		26.5±0.5	88.31*	66.39*	< 1
pH	7.442±0.003		7.443±0.005	7.483 ±0.004		7.497±0.005	91.99*	< 1	13.90*
V_D/V_T	0.24±0.02		0.20±0.03	0.24±0.03		0.21±0.03	<1	3.83	< 1
A-a DO_2	16.0±2.8		14.3±2.8	13.9±1.1		10.2±1.2	1.65	9.22*	< 1

Values are means ± SE. n = 16. *Significant at $P \leq 0.05$.

Table 4. Lung volumes, slope of phase III of the nitrogen washout curve, and transthoracic electrical impedance at low and high altitude.

Parameter	n	Phase						Variance Ratio		
		Low Altitude			High altitude					
		0 h	36 h	72 h	0 h	36 h	72 h	Altitude	Time	Interaction
Forced Vital Capacity(L)	20	5.45±0.18	5.45±0.19	5.46±0.19	5.38±0.20	5.42±0.19	5.39±0.19	7.35*	4.54*	< 1
Total lung capacity(L)	17	6.47±0.21	6.61±0.21	6.69±0.23	6.50±0.22	6.64±0.22	6.67±0.22	< 1	24.40*	< 1
Residual Volume (L)	17	1.26±0.06	1.33±0.05	1.34±0.05	1.29±0.05	1.43±0.05	1.49±0.06	26.81*	22.41*	19.14*
Closing Capacity (L)	17	1.77±0.09	1.81±0.07	1.87±0.09	1.76±0.07	1.90±0.08	2.03±0.08	8.52*	26.90*	5.71*
Slope of phase III (%N_2/L)	17	0.93±0.08	0.91±0.07	0.99±0.06	0.88±0.07	1.03±0.09	1.09±0.06	1.51	5.78*	3.17
Impedance (Ω/L)	17	3.98±0.17	3.87±0.16	3.83±0.17	3.62±0.16	3.54±0.12	3.61±0.14	28.79*	4.03*	2.60

Values are the mean ± SE. All volumes are corrected to BTPS conditions. *Significant at $P \leq 0.05$.

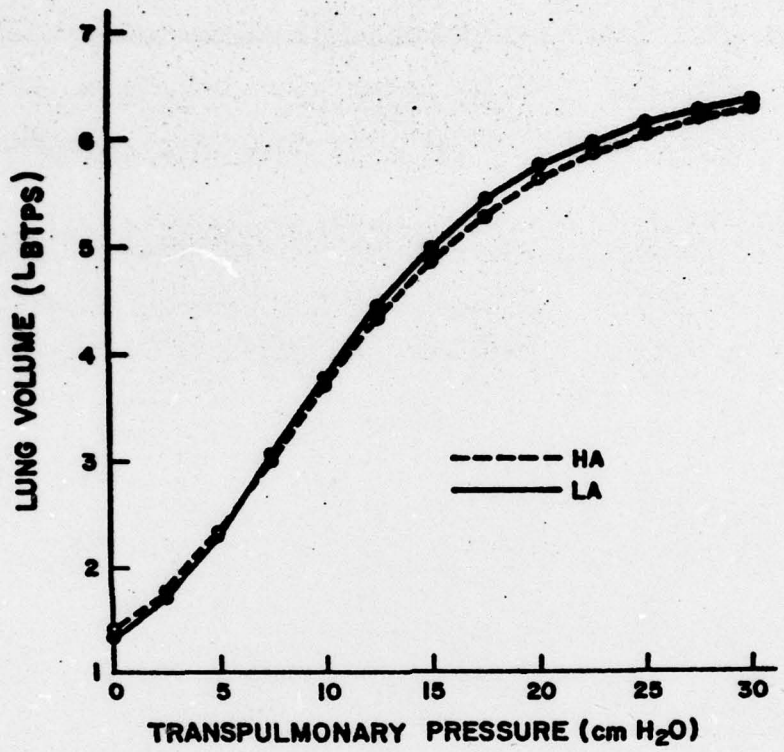

Figure 1. Mean expired limb of the quasi-static transpulmonary pressure–volume curve at low altitude (LA) and high altitude (HA). Each point is the mean of 33 observations, obtained from 11 subjects at 0, 36, and 72 h of each phase. The analysis of variance indicates that lung volume was a different function of transpulmonary pressure at high altitude than at low altitude ($p < 0.001$).